Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Mini Review

NEU3 (sialidase 3 (membrane sialidase))

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Identity

Other names: FLJ12388, SIAL3

HGNC (Hugo): NEU3

Location: 11q13.4

DNA/RNA

Description

The NEU3 gene spans 22 kb, consists of 4 exons and 3 introns. It is a member of sialidase family consisting of NEU1, NEU2, NEU3, and NEU4.

Transcription

Northern blot analysis reveals 2.5 kb and 7 kb transcripts of NEU3 gene, possessing a common open reading frame of 1284 bp. NEU3 gene expression is diversely regulated by Sp1/Sp3 transcription factors which are recently considered to play critical roles in regulating the transcription of genes involved in cell growth and tumorigenesis.

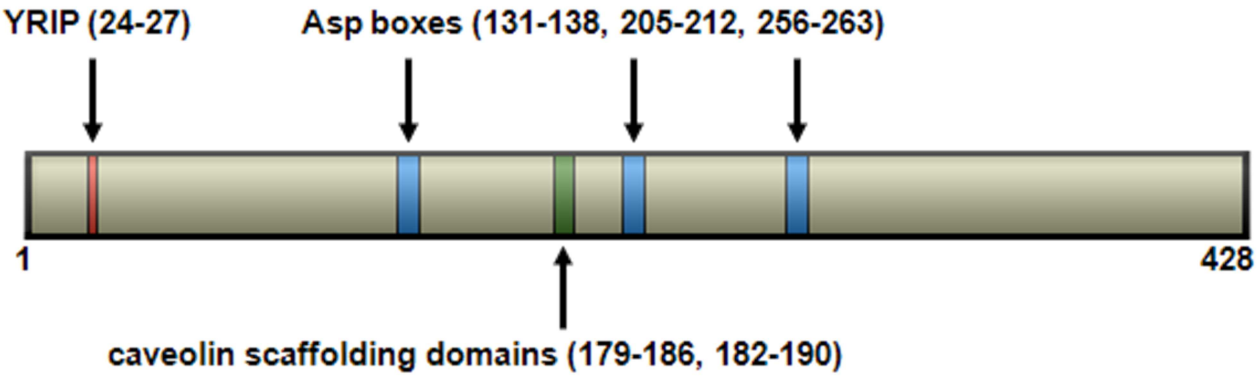
Protein

Description

Deduced amino acid sequence of human NEU3 comprises of 428 amino acids and contains RIP box at N-terminal region and three Asp boxes in the center of the amino acid sequence. These motifs are commonly found in sialidases of microorganisms and vertebrates. The RIP motif is a part of active site and mutation of this motif led to decreased enzymatic activity. The Asp box is thought to participate in proper 3D structure formation of NEU3.

Expression

The gene is ubiquitously expressed with relatively higher levels in skeletal muscle, heart, and testis. The expression is upregulated during tumorigenesis, neuronal differentiation, T cell activation, and monocyte differentiation. Abnormal upregulation of NEU3 is observed in various



human neoplasms including colon, renal, ovarian and prostate cancers, except for the down-regulation in acute lymphoblastic leukemia.
It is interesting to note that the transgenic mice ectopically expressing human NEU3 develop impaired insulin signaling and insulin-resistant diabetes mellitus by 18-22 weeks.

Localisation

Biochemical fractionation shows NEU3 to be localized in membrane fractions, especially in raft or caveolae membrane microdomains. In immuno- fluorescence studies, the bovine and mouse Neu3 sialidases are mostly detected on the cell surface, but the human NEU3 may exist also in other cellular membrane components and can mobilize to membrane ruffles together with Rac-1 in response to growth stimuli such as EGF, enhancing cell movement.

Function

NEU3 sialidase removes sialic acid moiety of gangliosides. It hardly acts on glycoproteins, oligosaccharides, and an artificial substrate 4MU-NeuAc. NEU3 alters gangliosides composition of tissues and cells, and leads to modulation of signal transduction such as EGFR (epidermal growth factor receptor) and IR (insulin receptor) signaling. Besides, NEU3 has been shown to associate with signaling molecules including EGFR, Grb2, caveolin-1, and Rac. In addition to the catalytic reaction as a sialidase, the interaction with the protein molecules may also give an influence on the NEU3 function. Disturbance of signaling by abnormal upregulation of NEU3 is likely a possible cause of tumorigenesis or diabetes mellitus.

Homology

The NEU3 amino acid sequence shows 28% identity to NEU1, 42% to NEU2, and 45% to NEU4. NEU3 orthologs are identified in bovine, mouse, and rat.

Implicated in

Colon cancer

Note

NEU3 shows higher enzymatic activity and mRNA level in colon tumors as compared to adjacent normal mucosa. In tumor cells, lactosylceramide, one of the products of NEU3 enzymatic reaction, accumulates in tumor cells. Over expression of NEU3 or exogenous addition of lactosylceramide to the cell culture confer resistance to sodium butyrate-induced apoptosis. On the other hand, silencing of NEU3 by siRNA causes induction of apoptosis in cancer cells accompanied with suppression of EGFR signaling, suggesting that survival of tumor cells is addictive to NEU3 expression. Interestingly, NEU3-knock down in normal cells including primary culture of keratinocytes or fibroblasts does not cause growth arrest nor apoptosis. Transgenic mice ectopically expressing human NEU3 shows upregulation of EGFR signaling, lower induction of apoptosis, and high incidence of ACF (aberrant crypt foci) formation in colon mucosa cells upon administration of azoxymethane (AOM), a carcinogen for colonic tumorigenesis.

Renal cell carcinoma

Note

Renal cell carcinoma shows upregulation of NEU3 along with high expression of IL6. IL6 appears to increase NEU3 gene expression in ACHN cells, and the increase brings about enhanced activation of PI3K and Akt upon IL6 administration, resulting in suppression of apoptosis.

Type II diabetes mellitus

Note

NEU3 transgenic mice develop impaired insulin signaling and insulin-resistant diabetes mellitus by 18-22 weeks, associated with hyper-insulinemia, islet hyperplasia and increase in the beta-cell mass. As compared to the wild type, insulin-stimulated phosphorylation of the insulin receptor and insulin receptor substrate I is significantly reduced, and activities of phosphatidylinositol 3-kinase and glycogen synthase are also decreased. In muscle extracts, association of tyrosine-phosphorylated NEU3 with Grb2 occurs in response to insulin, together with accumulation of ganglioside GM1 and GM2.
Involvement of NEU3 in cancer progression and development of diabetes suggests that these diseases might be closely related to each other in pathogenesis, given the recent epidemiological reports of higher cancer risk in diabetic patients than in controls.

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